

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

James Robl et al.

Group Art Unit: 1632

Application No. 09/260,468

Examiner: J. Martin

Filed: March 2, 1999

Title: EMBRYONIC OR STEM-LIKE CELL LINES PRODUCED BY CROSS-SPECIES NUCLEAR
TRANSPLANTATION AND METHODS FOR ENHANCING EMBRYONIC DEVELOPMENT BY
GENETIC ALTERATION OF DONOR CELLS OR BY TISSUE CULTURE CONDITIONS

* * * * *

AMENDMENT AND RESPONSE

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

In response to the Office Action dated June 21, 2001, please amend the above
identified application as follows.

*do not enter
5/25/02*

In the Claims

Please enter the following amended claim:

1. (Twice Amended) A method of producing embryonic stem-like cells, wherein said cells comprise a nucleus derived from an adult differentiated cell and mitochondria from an oocyte of a species other than said adult differentiated cell, comprising the following steps:

- B¹*
- (i) inserting a differentiated human or mammalian cell or cell nucleus into an enucleated animal oocyte, wherein such oocyte is derived from a different animal species than the human or mammalian cell under conditions suitable for the formation of a nuclear transfer (NT) unit;
 - (ii) activating the resultant nuclear transfer unit;
 - (iii) culturing said activated nuclear transfer unit until greater than the 2-cell developmental stage;
 - (iv) disassociating said activated nuclear transfer unit; and

*Amendment and Response*U.S. Serial No. 09/260,468Attorney Reference: 015837-0275817

Page 2

- β^1
- (v) isolating cells from said disassociated nuclear transfer unit to obtain embryonic stem-like cells.
-

See the attached Appendix for the changes made to effect the above claim(s).

Please add the following new claim(s):

β^2

--58. (New) The method of claim 1, wherein said cells isolated from said disassociated nuclear transfer unit are isolated from cells originating from the inner-most portion of said nuclear transfer unit.

59. (New) An embryonic stem-like cell isolated from the inner-most portion of a nuclear transfer unit according to the method of claim 58.

60. (New) The method of claim 1, wherein the adult cell inserted into the enucleated animal oocyte is a human cell, and the enucleated oocyte is a primate oocyte.

61. (New) The method of claim 53, wherein the adult cell inserted into the enucleated animal oocyte is a human cell, and the enucleated oocyte is a primate oocyte.--

*Amendment and Response*U.S. Serial No. 09/260,468Attorney Reference: 015837-0275817

Page 3

REMARKS

This Reply is responsive to the Office Action dated June 21, 2001. Entry of the foregoing and reconsideration on the merits pursuant to 37 CFR 1.112 is respectfully requested.

The application has been amended as set forth above. In accordance for the new rules for amending applications set forth in 37 CFR 1.121, which took effect on March 1, 2001, a marked up version of the claims showing all amendments is attached hereto as an appendix.

Specifically, claim 1 has been amended for grammatical purposes, and to emphasize the pluripotent nature of the embryonic stem-like cells obtained by the recited method. For instance, the specification makes clear at page 25, lines 17-19, that the embryonic stem-like cells of the invention are obtained out of a nuclear transfer unit, and as such could not be used for germ-line manipulation. New claim 58 further emphasizes the pluripotent nature of the embryonic stem-like cells obtained by the claimed methods by specifying that the cells are obtained from the inner-most portion of the nuclear transfer unit. Support for this claim may be found at page 34, lines 14-23. New claim 59 is directed to an embryonic stem-like cell isolated by the method of claim 58. And new claims 60 and 61 further limit claims 1 and 53, respectively, and specify that the adult cell inserted into the enucleated animal oocyte is a human cell, and the enucleated oocyte is a primate oocyte. Support for such claims may be found in the specification at page 19, line 8. No new matter has been added.

Turning now to the Office Action, the rejection of claims 18, 19 and 21-23 under 35 U.S.C. §101 has been maintained. According to the Office Action, the claims still fail to distinguish an embryonic stem-like cell from an embryonic cell that is a one, two or three cell embryo. Applicants respectfully maintain their traversal.

As discussed in the previous Reply filed April 11, 2001, the fact that nuclear transfer derived embryonic stem cells and the differentiated cells, tissues and animals derived therefrom retain the mitochondria from the enucleated recipient cell has been verified by several post-filing date references. For instance, Takeda et al. (1999) report "dominant distribution of mitochondrial DNA from recipient oocytes in bovine embryos and offspring after nuclear transfer" (see title and abstract). Evans et al. (1999) report that the mitochondrial DNA in the cloned sheep Dolly, as well as that in nine other nuclear transfer-derived sheep, was derived exclusively from recipient enucleated oocytes with no detectable

*Amendment and Response*U.S. Serial No. 09/260.468Attorney Reference: 015837-0275817

Page 4

contribution from respective somatic donor cells. These reports are consistent with observations gleaned from sexual mammalian fertilization, whereby the mitochondria derived from sperm are reportedly eliminated during early embryogenesis (see Kaneda et al., 1995; references are attached).

Thus, the embryonic stem-like cells produced by the claimed methods comprise a nucleus derived from an adult differentiated cell and mitochondria from an oocyte of species other than the adult differentiated cell. Such a distinction differentiates such cells from any other embryonic cell or embryo known in the art or in nature. According to the U.S. Supreme Court in Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980), the test for patentability under 35 U.S.C. §101 is whether the living matter is the result of human intervention. See also MPEP 2105. The point was also made in Chakrabarty that "Congress thus recognized that the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human made interventions." Applicants respectfully submit that an embryonic stem-like cell wherein the nuclear and mitochondrial DNAs are cross-species with regard to one another could only be a product of human intervention, and therefore, such cells satisfy the test set forth in Chakrabarty. Reconsideration and withdrawal of the rejection is respectfully requested.

Next, claims 1, 15, 16, 18, 19, 21-23, 32, 33, 35 and 51-57 stand rejected under 35 U.S.C. §112, first paragraph for alleged lack of enablement. The rejection is maintained for the reason that the specification fails to provide direction or guidance for the transplantation of a stem cell or cells differentiated therefrom containing exogenous mitochondria. Applicants respectfully disagree with the logic underlying the rejection as the claims are not directed to transplantation therapies. Moreover, other uses for the claimed cells were discussed in the previous amendment at the paragraph bridging pages 9-10.

Again, the generation of differentiated cells for transplantation is not the only utility for the nuclear transfer units generated by the claimed methods. For instance, on page 1 of the specification, Applicants note that embryonic stem cells provide an *in vitro* model for differentiation, and as such can be used to identify genes that are involved in the regulation of early development. Human cross-species ES-like cells in particular can be used to identify important human regulatory genes, and would be highly useful in this regard even if they were not used for transplantation purposes. Indeed, the fact that Applicants have found that

*Amendment and Response*U.S. Serial No. 09/260,468Attorney Reference: 015837-0275817

Page 5

cross-species nuclear transfer of a human cell into a bovine cell generates an activated nuclear transfer unit capable of division is an enormously exciting and important finding. For example, such cells provide a model for deciphering the role of the mitochondrial genome in mammalian development and cellular function.

Thus, Applicants believe that the activated cross-species nuclear transfer units and embryonic stem-like cells are fully enabled by the specification, and moreover have significant utility even if they are not used to produce differentiated cells and tissues for transplantation. However, Applicants respectfully emphasize that this does not mean that such activated nuclear transfer units could not be used to produce embryonic stem-like cells capable of being used for this purpose. Rather, Applicants believe the gaur data previously submitted demonstrates that cross-species nuclear transfer may be used to generate differentiated cells and tissues and even adult mammals. Furthermore, Applicants' success in producing primate stem cells demonstrates that there is no species barrier with regard to producing ES-like cells from activated oocytes that express primate DNA. Taken together with the gaur cross-species data, the primate stem cell data also suggests that cloned human differentiated cells may be produced using the methods disclosed in the specification using a phylogenetically similar recipient cell.

The Office Action states at page 5 that Applicants reliance on the gaur data and the generation of cross-species nuclear transfer units using donor and recipient cells that are phylogenetically related is irrelevant because the claims are not limited to phylogenetically similar species. In this regard, Applicants request consideration of new claims 60 and 61 above, where the claimed methods are limited to the use of human donor cells and primate recipient cells. Nevertheless, Applicants respectfully submit that the gaur data was submitted in order to demonstrate the feasibility of cross-species nuclear transfer to produce differentiated cells and tissues. The donor and recipient cells need not be phylogenetically similar, as demonstrated by the results reported in the specification that human cross-species nuclear transfer into a bovine oocyte generated a nuclear transfer unit with ES cell-like morphology.

In the previous Reply filed April 13, 2001, Applicants had pointed out that other applicants have not been held to the same strict standard of enablement as that advanced in the present prosecution. For instance, in U.S. Patent 6,200,806, Thomson was issued a claim

*Amendment and Response*U.S. Serial No. 09/260,468Attorney Reference: 015837-0275817

Page 6

directed to a pluripotent human embryonic stem cell line. The Examiner responds by noting that "pluripotency" in the Thomson patent is not an indication of "totipotency" (wherein totipotency means contribution to the germ line), in contrast to the present specification that discusses the use of the ES-like cells for germ line manipulation at pages 2-6.

Applicants respectfully note that the Examiner refers to the background of Applicants' specification which discusses the utility of ES cells as they were used in the prior art, not the specific goal of the present invention. Furthermore, it is clear from the specification at page 25, lines 17-19, for instance, that the nuclear transfer units of the present invention will be used to isolate pluripotent cells, not as a totipotent entity. Such totipotency is only realized upon implantation into a surrogate female, which is never suggested in the present application. In this regard, Applicants note that Thomson's pluripotent stem cell line was isolated from a totipotent entity as well (for instance, see the method recited in Claim 9 of the Thomson patent).

In order to emphasize the pluripotent nature of the cells (and distinguish them from totipotent entities), claim 1 has been amended above to clarify that the claimed embryonic stem-like cells are isolated from a disassociated nuclear transfer unit. More specifically, as recited in new claim 58, the cells are isolated from the "inner-most" portion of the nuclear transfer unit as discussed on page 34, lines 14-23, of the specification. While pluripotent cells may differentiate into all cell types of the body, they do not have the capability to generate an embryo when implanted into a surrogate female because the cells have differentiated past the stage where the trophectoderm forms. Thus, in view of the amendments to claim 1 above and particularly in view of new claim 58, it should now be clear that the cells of the invention are pluripotent rather than totipotent.

On page 7 of the Office Action, the Examiner rejects uses for the claimed cells other than for transplantation therapies, stating that model systems are not enabled by a specification that requires a need for delineation of the model system itself. In other words, the Examiner alleges that the claims find use in delineating their use, and mentions particularly the use of the cells as a model for deciphering the role of mitochondrial genes in mammalian development.

Applicants respectfully submit that the Examiner has provided no authority for this position so it is difficult for Applicants to analyze whether the present instance may be

*Amendment and Response*U.S. Serial No. 09/260,468Attorney Reference: 015837-0275817

Page 7

correlated to whatever case law the Examiner is using. However, Applicants assure that using the claimed ES-like cells as an entity for analyzing gene expression and mitochondrial contributions early in development does not require any delineation of the cells themselves, because the cells are produced by the methods disclosed in the specification. Once the cells exist, they may be used as models for assessing the role of mitochondria or mitochondrial genes or other genes in early embryonic development according to techniques known in the art at the time the invention was filed.

For instance, in 1993, Smith and Alcivar published a paper in J. Reprod. Fertil. Suppl. (abstract attached), reviewing research involving experiments with animals derived from reconstituted embryos, using nuclear or cytoplasmic transplantations, which suggested that nuclear-mitochondrial interactions are important but not essential in the survival and replication of exogenous mitochondria introduced into the egg. The abstract reports that in pig oocytes and embryos, mitochondria aggregate and are closely associated with endoplasmic reticulum, lipid granules and large vesicles. The showing that cross-species nuclear transplantation is possible and the isolation of ES-like cells wherein the nuclear and mitochondrial genomes are from different species will have important ramifications for these earlier observation.

The Smith and Alcivar abstract also reports that, although the direct correlation of mitochondrial genes with reproductive traits is still unclear, some human degenerative diseases and performance traits in cattle can be related directly to specific mtDNA polymorphisms, suggesting that cross-species ES-like cells may be important models for disease. As stressed in the abstract, "information on the transmission of mtDNA and its effects on performance will have many implications not only for our understanding of mitochondrial genetics but also for the increased productivity of animals." Thus, it is clear that the role of mitochondria and mitochondrial DNA during embryonic development is and was at the time the present application was filed an important area of research, and the claimed ES-like cells of the present invention would serve as an important contribution to that research outside of their use in transplantation therapies.

Finally, the Office Action rejects Applicants' arguments as to the fact that genetic modification of cells has been known in the art for years, and responds that genetic modification of the cells described in the present specification was not shown. As Applicants

*Amendment and Response*U.S. Serial No. 09/260,468Attorney Reference: 015837-0275817

Page 8

understand, the Examiner must present some basis, some tangible evidence, for doubting that generically modified cells could not be generated using the claimed cells. Indeed, such cells are no different than any other genetically modified cell previously known in the art but for the fact that the mitochondrial and nuclear genomes are from different species. In the absence of some reasonable basis to conclude that the cross-species nature of the mitochondrial and nuclear genomes would affect the amenability of the cells to being transfected, Applicants respectfully request reconsideration.

For all the above reasons, withdrawal of the enablement rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Finally, claims 1, 15, 16, 18, 19, 21-23, 32, 33, 35 and 51 remain rejected under the second paragraph of 35 U.S.C. §112, because the preamble of claim 1 recites embryonic "or" stem-like cells and Applicants speak only of embryonic stem-like cells. This rejection should now be moot in view of the amendment to the preamble of claim 1 entered above.

All issues raised by the Office Action dated April 10, 2001, have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that she contact the undersigned so that such issues may be addressed expeditiously.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached Appendix is captioned "Version with markings to show changes made".

All objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: 

Bonnie D. Weiss

Registration No. 43,255

1600 Tysons Boulevard
McLean, VA 22102
(703) 905-2000 Telephone
(703) 905-2500 Facsimile

*Amendment and Response*U.S. Serial No. 09/260,468Attorney Reference: 015837-0275817

Page 9

APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADEIn the Claims:

1 (Twice Amended) A method of producing embryonic [or] stem-like cells, wherein said cells comprise a nucleus derived from an adult differentiated cell and mitochondria from an oocyte of a species other than said adult differentiated cell, comprising the following steps:

- (i) inserting a differentiated human or mammalian cell or cell nucleus into an enucleated animal oocyte, wherein such oocyte is derived from a different animal species than the human or mammalian cell under conditions suitable for the formation of a nuclear transfer (NT) unit;
- (ii) activating the resultant nuclear transfer unit;
- (iii) culturing said activated nuclear transfer [units] unit until greater than the 2-cell developmental stage; [and
- (iv) culturing cells obtained from said cultured NT units to obtain embryonic stem-like cells]
- (iv) disassociating said activated nuclear transfer unit; and
- (v) isolating cells from said disassociated nuclear transfer unit to obtain embryonic stem-like cells.

PILLSBURY WINTHROP LLP



THE UNDERSIGNED HAVING BEEN INVOLVED IN THE ENVELOPING HEREBY CERTIFY THAT TODAY, September 21, 2001, ALL OF THE ITEMS REFERENCED ON PAGE(S) 1-9 OF THE CUSHMAN LOG OF ITEMS TO BE FILED IN THE PTO WERE PUT INTO A TOTAL OF 1 box ENVELOPE(S). FOR HAND CARRYING TO THE PTO BY ONE OF OUR COURIERS ON/AFTER 5:30 P.M. TODAY.

Sig.: David West
DOCKET CLERK

9/21/01 6:50
DATE TIME

Sig.: _____
DOCKET CLERK

DATE TIME

Sig.: _____
DOCKET CLERK

DATE TIME

I DO HEREBY CERTIFY THAT THE MAX DATE PROGRAM WAS RUN AND CHECKED.

Sig.: John Stewart
DOCKET CLERK

9-21-01
DATE TIME

I DO HEREBY CERTIFY THAT ON _____ I PICKED UP THE ABOVE TOTAL OF _____ ENVELOPE(S) AND HAND CARRIED SAME ON THAT DATE BEFORE MIDNIGHT TO THE UNITED STATES PATENT AND TRADEMARK OFFICE.

Sig.: _____
COURIER

DATE TIME

Pillsbury Winthrop LLP

September 21, 2001

Page: 1

Log of documents taken to PTO at 18:00 by _____

PATENTS

PATENTS

INVENTOR	SER #	DESCRIPTION	CHK #	AMOUNT	MAT #	ENTERED BY	AT
ARNOULD	9/869064	6-RESPONSE		\$ 0.00	281298	lxs	15:16
		ASSIGNMENT	136563	\$ 40.00		lxs	15:16
		DECLARATION	136563	\$ 130.00		lxs	15:16
		CLAIMS AND FEE	136563	\$ 270.00		lxs	15:17
		EXTENSION FEE	136563	\$ 110.00		lxs	15:17
		CHECK TOTAL		\$ 550.00			
BIESS	9/640915	1-AMENDMENT		\$ 0.00	268670	dgw	17:41
BLUM	9/463681	1-AMENDMENT		\$ 0.00	266043	lxs	15:20
		APPENDIX		\$ 0.00		lxs	15:21
CAIN	9/708702	ISSUE FEE	136606	\$ 1240.00	271023	mgw	17:45
		ASSIGNMENT	136606	\$ 40.00		mgw	17:45
		CHECK TOTAL		\$ 1280.00			
CAIN	9/879863	FILING FEE	136609	\$ 710.00	281424	dgw	17:52
		CLAIMS AND FEE	136609	\$ 270.00		dgw	17:52
		DECLARATION	136609	\$ 130.00		dgw	17:52
		ASSIGNMENT	136609	\$ 40.00		dgw	17:52
		CHECK TOTAL		\$ 1150.00			
CHEN	9/793400	20-REFILE ASSGT		\$ 0.00	276821	lxs	15:22
		ASSIGNMENT	136565	\$ 40.00		lxs	15:22
CHO	9/604040	1-AMENDMENT		\$ 0.00	274484	lxs	15:38
EIKKULA	9/856367	20-REFILE ASSGT		\$ 0.00	280285	lxs	15:32
		ASSIGNMENT		\$ 0.00		lxs	15:38
FODOR	8/325457	92-CONT PROS AP		\$ 0.00	275863	lxs	17:17
		PRELIM AMENDMNT		\$ 0.00		lxs	17:18
		APPENDIX		\$ 0.00		lxs	17:18
		CPA FILING FEE	136594	\$ 710.00		lxs	17:18
		EXTENSION FEE	136594	\$ 1890.00		lxs	17:18
		CHECK TOTAL		\$ 2600.00			
GAGNE	9/361528	REQ RETURN IDS		\$ 0.00	259139	dgw	17:15

Pillsbury Winthrop LLP

September 21, 2001

Page: 2

Log of documents taken to PTO at 18:00 by _____

PATENTS

PATENTS

INVENTOR	SER #	DESCRIPTION	CHK #	AMOUNT	MAT #	ENTERED BY	AT
HILL	9/876255	INF DISCLOSURE		\$ 0.00	280634	lxs	15:45
		DECLARATION	136568	\$ 130.00		lxs	15:44
		ASSIGNMENT	136568	\$ 40.00		lxs	15:44
		CHECK TOTAL		\$ 170.00			
HILL	9/897422	INF DISCLOSURE		\$ 0.00	278451	lxs	15:41
		DECLARATION	136567	\$ 130.00		lxs	15:40
		FILING FEE	136567	\$ 710.00		lxs	15:41
		CHECK TOTAL		\$ 840.00			
JACKSON	9/647876	PRELIM AMENDMNT		\$ 0.00	268585	dgw	17:13
		CLAIMS AND FEE	136592	\$ 80.00		dgw	17:13
JIMENEZ	9/852051	INF DISCLOSURE		\$ 0.00	278455	lxs	15:31
KANEKO	9/609431	INF DISCLOSURE	136608	\$ 180.00	271482	mgh	17:49
KANEYAMA	9/523463	92-CONT PROS AP		\$ 0.00	257759	dgw	17:17
		PRELIM AMENDMNT		\$ 0.00		dgw	17:18
		CPA FILING FEE	136593	\$ 710.00		dgw	17:17
KAWAMURA	9/532309	ADDRESS CHANGE		\$ 0.00	258078	lxs	15:19
		ISSUE FEE	136564	\$ 1240.00		lxs	15:20
KIM	9/542649	1-AMENDMENT		\$ 0.00	274462	lxs	15:39
KOJIMA	9/324118	1-AMENDMENT		\$ 0.00	260291	mgh	17:47
		APPENDIX		\$ 0.00		mgh	17:47
KOMURA	9/816143	SUPPLE IDS		\$ 0.00	277994	mgh	17:50
LANSBERGEN	9/709319	ISSUE FEE	136604	\$ 1240.00	274498	mgh	17:44
		ASSIGNMENT	136604	\$ 40.00		mgh	17:44
		CHECK TOTAL		\$ 1280.00			
LEE	9/603440	1-AMENDMENT		\$ 0.00	274481	lxs	15:40
MASON	9/870586	6-RESPONSE		\$ 0.00	264782	lxs	17:46
		FORMAL DRAWINGS		\$ 0.00		lxs	17:46
		INF DISCLOSURE		\$ 0.00		lxs	17:46

Pillsbury Winthrop LLP

September 21, 2001

Page: 3

Log of documents taken to PTO at 18:00 by _____

PATENTS

PATENTS

INVENTOR	SER #	DESCRIPTION	CHK #	AMOUNT	MAT #	ENTERED BY	AT
OHMI	9/866576	FORMAL DRAWINGS		\$ 0.00	281355	1xs	16:51
		PRELIM AMENDMNT		\$ 0.00		1xs	16:51
		APPENDIX		\$ 0.00		1xs	16:51
		FILING FEE	136586	\$ 710.00		1xs	16:50
		DECLARATION	136586	\$ 130.00		1xs	16:50
		ENGLISH SPEC'N	136586	\$ 130.00		1xs	16:51
		CLAIMS AND FEE	136586	\$ 342.00		1xs	16:51
		CLAIMS AND FEE	136586	\$ 1120.00		1xs	16:51
		ASSIGNMENT	136586	\$ 40.00		1xs	16:51
CHECK TOTAL				\$ 2472.00			
PETTERSEN	9/ 90953	92-CONT PROS AP		\$ 0.00	251491	1xs	16:54
		PRELIM AMENDMNT		\$ 0.00		1xs	16:54
		EXTENSION FEE	136588	\$ 445.00		1xs	16:54
		CPA FILING FEE	136588	\$ 355.00		1xs	16:55
		SUSPEND 3 MOS	136588	\$ 130.00		1xs	16:56
		CHECK TOTAL				\$ 930.00	
REESE	9/485606	1-AMENDMENT		\$ 0.00	266225	dgw	17:42
		CHANGE ADDRESS		\$ 0.00		dgw	17:43
		APPENDIX		\$ 0.00		dgw	17:43
		CLAIMS AND FEE	136603	\$ 162.00		dgw	17:42
		CLAIMS AND FEE	136603	\$ 480.00		dgw	17:42
		EXTENSION FEE	136603	\$ 110.00		dgw	17:43
		INF DISCLOSURE	136603	\$ 180.00		dgw	17:43
		CHECK TOTAL				\$ 932.00	
RICHARDSON	9/868594	6-RESPONSE		\$ 0.00	281381	dgw	17:45
		CHANGE ADDRESS		\$ 0.00		dgw	17:46
		CLAIMS AND FEE	136607	\$ 270.00		dgw	17:45
		DECLARATION	136607	\$ 130.00		dgw	17:45
		ASSIGNMENT	136607	\$ 40.00		dgw	17:45
		CHECK TOTAL				\$ 440.00	
RIEPING	9/801042	SEQUENCE LIST		\$ 0.00	278410	1xs	17:00
		DISK		\$ 0.00		1xs	17:00
		FORMAL DRAWINGS		\$ 0.00		1xs	17:00
		PRIORITY DOC		\$ 0.00		1xs	17:00
		ENGLISH SPEC'N	136590	\$ 130.00		1xs	16:59

Pillsbury Winthrop LLP

September 21, 2001

Page: 4

Log of documents taken to PTO at 18:00 by _____

PATENTS

PATENTS

INVENTOR	SER #	DESCRIPTION	CHK #	AMOUNT	MAT #	ENTERED BY	AT
		DECLARATION	136590	\$ 130.00		1xs	17:00
		ASSIGNMENT	136590	\$ 40.00		1xs	17:00
		FILING FEE	136590	\$ 710.00		1xs	17:00
		CLAIMS AND FEE	136590	\$ 180.00		1xs	17:00
		CLAIMS AND FEE	136590	\$ 480.00		1xs	17:00
		CLAIMS AND FEE	136590	\$ 270.00		1xs	17:01
		CHECK TOTAL		\$ 1940.00			
ROBL	9/260468	1-AMENDMENT		\$ 0.00	275817	1xs	16:57
		APPENDIX		\$ 0.00		1xs	16:58
		CLAIMS AND FEE	136589	\$ 27.00		1xs	16:58
SALIN	8/668828	CERT CORREC		\$ 0.00	224369	mgh	17:50
SHIFRIN	9/633070	1-AMENDMENT		\$ 0.00	268644	1xs	15:26
		APPENDIX		\$ 0.00		1xs	15:26
		INF DISCLOSURE	136566	\$ 180.00		1xs	15:27
		EXTENSION FEE	136566	\$ 55.00		1xs	15:27
		CHECK TOTAL		\$ 235.00			
SHOU	8/262059	CERTIF CORREC	136587	\$ 100.00	205469	1xs	16:52
		PET 1.183	136587	\$ 130.00		1xs	16:52
		CHECK TOTAL		\$ 230.00			
ST JOHN	9/482562	FORMAL DRAWINGS		\$ 0.00	259064	1xs	15:49
		ISSUE FEE	136569	\$ 1240.00		1xs	15:49
STOLL	9/534325	INF DISCLOSURE		\$ 0.00	257550	1xs	15:25
TOYOSHIMA	9/357829	5-NTC OF APPEAL		\$ 0.00	262687	dgw	17:53
		APPEAL FEE	136610	\$ 310.00		dgw	17:54
		EXTENSION FEE	136610	\$ 110.00		dgw	17:54
		CHECK TOTAL		\$ 420.00			
TUUNANEN	9/381270	1-AMENDMENT		\$ 0.00	263338	dgw	17:00
		APPENDIX		\$ 0.00		dgw	17:00
YAMANASHI	9/499608	ADDRESS CHANGE		\$ 0.00	266210	1xs	15:11
		ISSUE FEE	136562	\$ 1240.00		1xs	15:12

Pillsbury Winthrop LLP

September 21, 2001

Page: 5

Log of documents taken to PTO at 18:00 by _____

PATENTS

PATENTS

INVENTOR	SER #	DESCRIPTION	CHK #	AMOUNT	MAT #	ENTERED BY AT
----------	-------	-------------	-------	--------	-------	------------------

PATENT TOTAL

\$ 20226.00

Pillsbury Winthrop LLP

September 21, 2001

Page: 1

Log of documents taken to PTO at 18:00 by _____

NEW APPLICATIONS

NEW APPLICATIONS

INVENTOR	SER #	DESCRIPTION	CHK #	AMOUNT	MAT #	ENTERED BY	AT
BOETTCHER	/	NEW APPLICATION		\$ 0.00	271811	lxs	16:01
		INF DISCLOSURE		\$ 0.00		lxs	16:03
		FORMAL DRAWINGS		\$ 0.00		lxs	16:03
		DECLARATION		\$ 0.00		lxs	16:03
		ENGLISH SPEC'N		\$ 0.00		lxs	16:03
		ASSIGNMENT	136585	\$ 40.00		lxs	16:03
		CLAIMS AND FEE	136585	\$ 40.00		lxs	16:03
		FILING FEE	136585	\$ 355.00		lxs	16:04
		CHECK TOTAL		\$ 435.00			
BOOTH	/	NEW APPLICATION		\$ 0.00	283727	lxs	17:13
		FORMAL DRAWINGS		\$ 0.00		lxs	17:13
		ENGLISH SPEC'N		\$ 0.00		lxs	17:13
BOOTH	/	NEW APPLICATION		\$ 0.00	283728	lxs	17:17
		FORMAL DRAWINGS		\$ 0.00		lxs	17:17
		ENGLISH SPEC'N		\$ 0.00		lxs	17:17
HEINEN	/	NEW APPLICATION		\$ 0.00	282982	dgw	17:32
		ENGLISH SPEC'N		\$ 0.00		dgw	17:32
		DECLARATION		\$ 0.00		dgw	17:32
		INF DISCLOSURE		\$ 0.00		dgw	17:33
		PRELIM AMENDMNT		\$ 0.00		dgw	17:34
		APPENDIX		\$ 0.00		jeh	18:22
		ASSIGNMENT	136597	\$ 40.00		dgw	17:32
		FILING FEE	136597	\$ 710.00		dgw	17:34
		CHECK TOTAL		\$ 750.00			
HEMME	/	NEW APPLICATION		\$ 0.00	282979	lxs	15:52
		PRIORITY DOC		\$ 0.00		lxs	15:52
		FORMAL DRAWINGS		\$ 0.00		lxs	15:52
		ENGLISH SPEC'N		\$ 0.00		lxs	15:52
LUO	9/244722	PET'N TO EXTEND	136591	\$ 445.00	259867	lxs	17:01
LUO	/	NEW APPLICATION		\$ 0.00	283695	lxs	17:11
		FORMAL DRAWINGS		\$ 0.00		lxs	17:11
		ENGLISH SPEC'N		\$ 0.00		lxs	17:11
		INF DISCLOSURE		\$ 0.00		lxs	17:11
NISHIOKA	/	NEW APPLICATION		\$ 0.00	283651	dgw	17:21
		ENGLISH SPEC'N		\$ 0.00		dgw	17:21

Pillsbury Winthrop LLP

September 21, 2001

Page: 2

Log of documents taken to PTO at 18:00 by _____

NEW APPLICATIONS

NEW APPLICATIONS

INVENTOR	SER #	DESCRIPTION	CHK #	AMOUNT	MAT #	ENTERED BY	AT
		FORMAL DRAWINGS		\$ 0.00		dgw	17:22
		INF DISCLOSURE		\$ 0.00		dgw	17:22
NURMELA	/	NEW APPLICATION		\$ 0.00	283740	1xs	17:22
		FORMAL DRAWINGS		\$ 0.00		1xs	17:22
		DECLARATION		\$ 0.00		1xs	17:23
		INF DISCLOSURE		\$ 0.00		1xs	17:23
		ENGLISH SPEC'N		\$ 0.00		1xs	17:23
		ASSIGNMENT	136595	\$ 40.00		1xs	17:23
		CLAIMS AND FEE	136595	\$ 960.00		1xs	17:23
		FILING FEE	136595	\$ 710.00		1xs	17:23
		CHECK TOTAL		\$ 1710.00			
UDREA	/	NEW APPLICATION		\$ 0.00	283025	1xs	17:30
		INF DISCLOSURE		\$ 0.00		1xs	17:30
		ENGLISH SPEC'N		\$ 0.00		1xs	17:31
		DECLARATION		\$ 0.00		1xs	17:31
		FORMAL DRAWINGS		\$ 0.00		1xs	17:31
		SMALL ENTITY		\$ 0.00		1xs	17:32
		ASSIGNMENT	136596	\$ 40.00		1xs	17:30
		CLAIMS AND FEE	136596	\$ 522.00		1xs	17:32
		CLAIMS AND FEE	136596	\$ 80.00		1xs	17:32
		FILING FEE	136596	\$ 355.00		1xs	17:32
		CHECK TOTAL		\$ 997.00			
UDREA	/	NEW APPLICATION		\$ 0.00	283026	mgh	17:35
		ENGLISH SPEC'N		\$ 0.00		mgh	17:36
		DECLARATION		\$ 0.00		mgh	17:36
		FORMAL DRAWINGS		\$ 0.00		mgh	17:36
		INF DISCLOSURE		\$ 0.00		mgh	17:36
		FILING FEE	136599	\$ 355.00		mgh	17:35
		CLAIMS AND FEE	136599	\$ 36.00		mgh	17:35
		ASSIGNMENT	136599	\$ 40.00		mgh	17:35
		CHECK TOTAL		\$ 431.00			
WILSON	/	NEW APPLICATION		\$ 0.00	268456	dgw	18:03
		PRELIM AMENDMNT		\$ 0.00		dgw	18:03
		ENGLISH SPEC'N		\$ 0.00		dgw	18:03
		DECLARATION		\$ 0.00		dgw	18:03
		FORMAL DRAWINGS		\$ 0.00		dgw	18:04
		INF DISCLOSURE		\$ 0.00		dgw	18:04

Pillsbury Winthrop LLP

September 21, 2001

Page: 3

Log of documents taken to PTO at 18:00 by _____

NEW APPLICATIONS

NEW APPLICATIONS

INVENTOR	SER #	DESCRIPTION	CHK #	AMOUNT	MAT #	ENTERED	
						BY	AT
		ASSIGNMENT	136611	\$ 40.00		dgw	18:04
		IPER	136611	\$ 100.00		dgw	18:05
		CHECK TOTAL		\$ 140.00			
YANTOVSKY	/	NEW APPLICATION		\$ 0.00	283738	mgh	17:39
		PRELIM AMENDMNT		\$ 0.00		mgh	17:39
		ENGLISH SPEC'N		\$ 0.00		mgh	17:39
		INF DISCLOSURE		\$ 0.00		mgh	17:40
		FORMAL DRAWINGS		\$ 0.00		mgh	17:40
		FILING FEE	136601	\$ 430.00		mgh	17:39
		NEW APP. TOTAL		\$ 5338.00			

Pillsbury Winthrop LLP

September 21, 2001

Page: 1

Log of documents taken to PTO at 18:00 by _____

TRADEMARKS

TRADEMARKS

OWNER	SER #	DESCRIPTION	CHK #	AMOUNT	MAT #	ENTERED	
						BY	AT
AMERICAN BIOPHY	/	TM NEW APPLCATN		\$ 0.00	284000	1xs	17:45
		DRAWING		\$ 0.00		1xs	17:45
		TM SIGNED DECL		\$ 0.00		1xs	17:45
		TM FILING FEE	136605	\$ 325.00		1xs	17:45
BLAIR CORPORATI	73/658667	52 - S.8 DEC		\$ 0.00	60474	1xs	17:35
		53 - RNWL APPN		\$ 0.00		1xs	17:35
		TM SPECIMEN		\$ 0.00		1xs	17:36
		TM SIGNED DECL	136598	\$ 100.00		1xs	17:35
		RWNL FEE	136598	\$ 400.00		1xs	17:36
		CHECK TOTAL		\$ 500.00			
BOMBARDIER INC	/	TM NEW APPLCATN		\$ 0.00	282545	1xs	17:42
		DRAWING		\$ 0.00		1xs	17:42
		TM SIGNED DECL		\$ 0.00		1xs	17:42
		TM FILING FEE	136602	\$ 325.00		1xs	17:42
KAO KABUSHIKI K	72/334555	P O A		\$ 0.00	91278	1xs	17:39
		DESIGN REP		\$ 0.00		1xs	17:39
		TM ASGNMENT FEE	136600	\$ 40.00		1xs	17:39
PANACYA, INC	78/ 28025	1-AMENDMENT		\$ 0.00	282542	1xs	17:36
		P O A		\$ 0.00		1xs	17:36
		ADDRESS CHANGE		\$ 0.00		1xs	17:36
WEBVERSA INC	76/180031	1-AMENDMENT		\$ 0.00	273158	1xs	17:34
		SUBST DRAWING		\$ 0.00		1xs	17:34
TRADEMARK TOTAL							\$ 1190.00

Pillsbury Winthrop LLP

September 21, 2001

Page: 1

Log of documents taken to PTO at 18:00 By _____

MAINTENANCE FEES

MAINTENANCE FEES

PATENT #	SER #	DESCRIPTION	CHK #	AMOUNT	MAT #	ENTERED	
						BY	AT
4930158	7/237175	MAINTENANCE FEE	136570	\$ 1495.00	64618	jal	15:59
4930160	7/237176	MAINTENANCE FEE	136571	\$ 1495.00	204105	jal	15:59
5321126	7/913750	MAINTENANCE FEE	136580	\$ 1950.00	95175	jal	16:00
5328670	7/854565	MAINTENANCE FEE	136573	\$ 1950.00	95034	jal	15:59
5336527	7/797952	MAINTENANCE FEE	136572	\$ 1950.00	93455	jal	15:59
5736180	8/507242	MAINTENANCE FEE	136581	\$ 850.00	219392	jal	16:00
5738864	8/602733	MAINTENANCE FEE	136582	\$ 850.00	220860	jal	16:00
5747114	8/710476	MAINTENANCE FEE	136584	\$ 850.00	241953	jal	16:00
5756852	8/730206	MAINTENANCE FEE	136583	\$ 425.00	224810	jal	16:00
5758546	8/640470	MAINTENANCE FEE	136579	\$ 850.00	223438	jal	16:00
5765445	8/688798	MAINTENANCE FEE	136578	\$ 850.00	222952	jal	16:00
5780969	8/510655	MAINTENANCE FEE	136574	\$ 850.00	219352	jal	15:59
5782946	8/593920	MAINTENANCE FEE	136575	\$ 850.00	220664	jal	16:00
5784253	8/893016	MAINTENANCE FEE	136577	\$ 850.00	234533	jal	16:00
5790569	8/631426	MAINTENANCE FEE	136576	\$ 850.00	223287	jal	16:00

MAINT FEE TOTAL

\$ 16915.00

PILLSBURY WINTHROP LLP

1600 TYSONS BOULEVARD
MCLEAN, VIRGINIA 22102
(703) 905-2000

No. 136589

18-120
540

PAY

TO THE ORDER OF Director of the U. S. Patent and Trademark OfficeSeptember 21, 2001Twenty-seven dollars and 00 cents\$ *****27.00

Serial No. 09/260468

U.S. PATENT AND TRADEMARK FEES ACCOUNT

Bank of America
WASHINGTON, D. C.

Margaret S. Jackson

⑈136589⑈ ⑆054001204⑆ 1920814058⑈

⑈0000002700⑈

Apr-23-2002 16:51

From-PILLSBURY WINTHRP

T-963

P.028/028

F-666

PATENT AND TRADEMARK OFFICE
12-10-001
09-24-2001
FOR CREDIT TO THE
U.S. TREASURY

2026 47073

FIRST VINCENNA BANK
402 WEST 10TH AVE.
VINCENNA, IN 47591
FED. RES. BANK
P-056 OCT 1 1994

SEP 25 01

BANK OF AMERICA NA BAL
056007387 E2988 18 P64
09/25/01

3510570255

VS DATE 09/25/01
P01 E C 664

#15
attachment

J Reprod Fertil Suppl 1993;48:31-43

Related Articles. Books**Cytoplasmic inheritance and its effects on development and performance.****Smith LC, Alcivar AA.**

Centre de Recherche en Reproduction Animale, Faculte de Medecine Veterinaire, Universite de Montreal, Saint-Hyacinthe, QC, Canada.

In contrast to nuclear inheritance, cytoplasmic inheritance in mammals is derived mostly, if not exclusively, from the maternal line. Mitochondria, and their DNA molecules (mtDNA), are the genetic units of this method of inheritance. Mammalian mtDNA codes for 13 enzymes used in the mitochondrial energy-generating pathway, oxidative phosphorylation, 22 tRNAs and two rRNAs. Although all transcripts of mtDNA and their translational products remain in the mitochondria, most proteins used in mitochondria are from nuclear DNA and are imported after synthesis on cytoplasmic ribosomes. Spermatozoa introduce a small number of mitochondria into the cytoplasm of the egg at fertilization, which appear to be digested soon after penetration. Although the paternal contribution of mtDNA to the offspring is not believed to occur in mammals, some interspecific crosses have suggested that it does occur. Experiments with animals derived from reconstituted embryos, using nuclear or cytoplasmic transplantations, suggest that nuclear-mitochondrial interactions are important but not essential in the survival and replication of exogenous mitochondria introduced into the egg. As the levels of heteroplasmy varied in several tissues of animals derived from reconstituted embryos, it is suggested that differential partitioning of mitochondria occurs during embryogenesis. Mitochondrial morphology changes substantially during oogenesis and throughout early cleavage stages. Somatic morphology and normal replication patterns are regained at the blastocyst stage. In pig oocytes and embryos, mitochondria aggregate and are closely associated with endoplasmic reticulum, lipid granules and large vesicles. Although the direct correlation of mitochondrial genes with reproductive traits is still unclear, some human degenerative diseases and performance traits in cattle can be related directly to specific mtDNA polymorphisms. In pigs, reciprocal-cross comparisons have indicated greater offspring parent similarity with dam than sire for lean:fat ratio. A difference was also observed for oxygen consumption and oxidative phosphorylation, but not for anaerobic energy metabolism, in a pig reciprocal-cross experiment. Information on the transmission of mtDNA and its effects on performance will have many implications not only for our understanding of mitochondrial genetics but also for the increased productivity of animals. There are also potential ramifications to the animal cloning industry.